REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 6-8 and 69 are currently pending. Amendment to claim 1 is made for clarification purpose only and does not constitute new matter.

II. Rejection under 35 USC §101

Claim 1, 6-8, and 69 stand rejected under 35 U.S.C. §101 on the ground that the claimed invention allegedly is not supported by either a specific, substantial, and credibly asserted utility or a well established utility. Applicants respectfully traverse the rejection.

Specifically, the Action acknowledges that the specification teaches modified dCK (SEQ ID NO:5) having enhanced kinase activity to phosphorylate nucleoside analogs such as AraC. The Action also acknowledges that the dCK-antibody conjugate is internalized into the cell via specific antibody-antigen interaction. The Action further acknowledges that, once inside the cell, the conjugate increases the efficacy of nucleoside analogs in killing cells by phosphorylating the analog. Nevertheless, the Action asserts that the claimed conjugate lacks a specific, substantial and credible utility, such as the utility of treating cancer, because the specification allegedly "does not teach whether or how the conjugate works in order to achieve the purpose." The allegation seems to stem from the Office's assumption that only nuclear dCK is effective in killing cancer cells. Applicants respectfully traverse the rejection.

According to MPEP 2107 II, to properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the clamed invention lacks utility, and (B) provide sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing. A *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:

> (1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;
>
> (2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Applicants submit that the Office has failed to make a *prima facie* showing of lack of utility because, *inter alia*, the Office failed to provide sufficient evidentiary basis for whatever factual assumptions were relied upon in promulgating the rejection. The Action asserts that the specification does not show whether or how the conjugate works because it does not show whether or how the conjugate penetrates the nuclear membrane. The Action bases its rejection on the assumption that the phosphorylation processes "seem to occur inside the nucleus, not in the cytoplasm of the cells." However, the Action failed to provide any evidentiary basis for the factual assumption relied upon in making this assertion.

Applicants believe that this failure is fatal to the asserted utility rejection, and contend that it must be withdrawn on this basis alone. Despite the fact that Applicants believe the Office has not made a *prima facie* showing of lack of utility, the Applicants submit the following arguments with respect to the specific and substantial utility of the claimed invention.

Specific Utility

An invention has specific utility if the identified use or application is specific to the subject matter claimed. Assertions that disclose a specific biological activity and reasonably correlate that activity to a disease condition are sufficient to identify specific utility. MPEP 2107.01 I A. The claimed dCK-antibody conjugate comprises a modified dCK with enhanced nucleoside kinase activity. It is recognized in the Action that this enhanced nucleoside kinase activity permits the modified cDK enzyme to more efficiently phosphorylate nucleoside analogs, such as AraC, that are known to have cytostatic and cytotoxic activities against cancer cells. The antibody recognizes an antigen expressed predominantly in cancer cells, and targets the conjugate to the cancer cells. Thus, the conjugate can be used to specifically kill cancer cells. The disclosure of a specific use to treat a specific disorder (cancer) is clearly distinguishable from "situations where the applicant merely indicates that an invention may prove useful without identifying with specificity why it <u>is</u> considered useful…or indicating that a compound may be useful in treating unspecified disorders." *Id.*

(Emphasis original) Hence, the claimed conjugate and pharmaceutical composition comprising the conjugate do have specific utility.

Substantial utility

A claimed invention has substantial utility if it defines a "real world" use. The Court of Customs and Patent Appeals states that "[p]ractical utility is a shorthand way of attributing 'real world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." MPEP 2107.01 I. (*citing Nelson v Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980).)

1. The conjugate phosphorylates AraC and enhances the toxicity of AraC in killing cancer cells.

The specification discloses, and the Action admits, that the conjugate is used in treating cancer. The claimed conjugate thus provides an immediate benefit to the public and has a real world use and substantial utility. The Action nevertheless alleges that the disclosure does not teach whether or how the conjugate works in order to kill cancer cells. The Action refers to Figure 9 and alleges that the specification does not provide enough convinced evidence to support that the conjugate enhances the toxicity of AraC. The Action thus asserts that further research and experimentation is required to form a useful treatment. Applicants respectfully disagree.

The Office's reliance on Figure 9 for its assertion that the specification does not teach whether the conjugate works to kill cancer cells is misplaced. The negative results in Figure 9 demonstrate the conjugate's specificity for CD33 expressing cancer cells. As expected, the conjugate has no effect on CD33 negative 293T cells. See Figure 9. On the other hand, in CD33 expressing cells, the conjugate increases the percentage of apoptosis in cells treated with both AraC and the conjugate, compared to cells treated with AraC alone. See Figure 8. Thus, the conjugate has substantial utility because it enhances the toxicity of AraC in CD33-expressing cancer cells and confers a real world benefit of treating cancer.

This result is exemplary rather than limiting, so that one with skill in the art would understand and appreciate that the distinction between the cells killed by the conjugate and the cells not killed by the conjugate is the different in surface antigen expression, so that the

invention is not limited to CD33 expressing cells but encompassed any cancer-specific cell surface antigen.

2. It is not incumbent on the Applicant to prove operativeness when the mode of operation is readily understood and when the Office presents no contradicting evidence.

The Action further asserts that the specification does not teach how the conjugate works to treat cancer cells. The Action acknowledges that the conjugate is internalized inside the cell, but nevertheless asserts that further research is required to determine whether or how the internalized dCK conjugate penetrates the nuclear membrane to phosphorylate nucleoside analogs.

The Court of Customs and Patent Appeals has held that, "in the usual case where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry, operativeness is not questioned, and no further evidence is required." *In re Gazave*, 154 USPQ 92, 96 (CCPA 1967). The Gazave court stated that "[i]n the absence of any apparent reason why the compounds disclosed will not so function, or of any evidence showing that they actually do not, the statements in the application are generally deemed sufficient." *Id.* (*citing Bluestone v. Schmerling*, 121 U.S.P.Q. 417, 420 (C.C.P.A. 1959).)

With respect to utility, the court explicitly rejected the position that it is incumbent on the applicant to come forward with evidence that the compounds will function as stated in the application. *Id.* The court recognized in some situations, for example, if the alleged operation seems clearly to conflict with a recognized scientific principles, or where the device involved was of such a nature that it could not be tested by any known scientific principles, it would be incumbent on the applicant to demonstrate the workability and utility of the device and make clear the principles on which it operates. *Id.*

The court in *Gazave* reversed the Office's utility rejection because the applicant's assertions were believable, and the examiner did not presented evidence contradicting the assertions and evidence of operativeness presented in the application. *Id.* at 96-97. Further, the court held that the Office improperly sought to require too much proof of the asserted usefulness of the invention since the invention at issue did not appear to be of such a speculative or esoteric nature that it must inherently be considered unbelievable. *Id.* at 96.

In the instant application, no further evidence of operativeness is required because the claimed invention conforms to the known principles in the art and can be readily understood by one of skill in the art. The specification determines the structure of dCK, teaches the modified dCK with enhanced kinase activity, demonstrates specific targeting of the conjugate to CD33 expressing cells, and shows increased cytotoxicity of AraC in cells treated with the conjugate. Simply stated, Applicants demonstrated that the invention works, i.e., it increases cytotoxicity in cancer-specific cell surface antigen expressing cancer cells, and it is unnecessary for Applicants to provide method or mechanism explaining how the invention works.

Further, the utility rejection is improper because the invention at issue is not of such a speculative or esoteric nature that it must inherently be considered unbelievable. Thus, it is not incumbent on Applicants to come forward with further evidence to show the exact mechanism as to where the conjugate works to inhibit tumor growth. Similar to Gazave, the specification provides sufficient and credible basis supporting the substantial utility, and no further evidence should be deemed necessary to prove operativeness.

Additionally, the Action has not set forth any reason why the conjugate internalized inside the cell would not work to kill cancer cells, which is particularly significant because the invention shows the exact opposite - that the exemplary conjugates do in fact increase cytotoxicity of AraC. Nor has the Action presented any evidence showing that the conjugate does not actually function as stated. On the contrary, the very art cited in the Action contradicts the assertions supporting the utility rejection in the Action. It was known in the art that dCK kills cancer cells in the presence of AraC. See Zhu *et al.*, 2000, *J. Biol. Chem.* 275: 26727-26731. Zhu *et al.* teach that AraC phosphorylated by either dCK destined for nucleus (nucDCK-GFP) or by dCK retained in the cytosol (cytDCK-GFP) can be efficiently incorporated into nuclear DNA and cause cell death. See page 26728, right column, 3rd paragraph, to page 26729, left column, first paragraph, and Figure 3. Zhu *et al.* also teach that the cells expressing either nuclear or cytosolic dCK exhibited increased sensitivity to nucleoside analogs and a reduced IC_{50} for the analogs by 50- to 400-fold compared to dCK negative cells. See Figure 4. Further, Zhu *et al.* teach that nucDCK-GFP and cytDCK-GFP increase sensitivity of the cells to nucleoside analog to similar levels. See page 26729, paragraph bridging the left and the right columns. Thus, one skilled artisan would understand

that, once dCK is internalized inside the cell, no further research is required to determine whether the dCK enzyme enters nucleus to phosphorylate nucleoside analog and kill cancer cell.

Thus, as in *Gazave*, the utility rejection here is improper because the Office has not presented any evidence contradicting the evidence presented in the specification. The Action has failed to support its assertion that further research and experimentation is required to form a useful and practical treatment.

Based on the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §101.

III. Rejection under 35 USC §112, Second Paragraph

Claims 1, 6-8 and 69 stand rejected under 35 USC §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Action asserts that the term "an amino acid sequence identified as SEQ ID NO:5" is indefinite because it reads on a fragment as small as two amino acid peptide fragment of SEQ ID NO:5. Applicants traverse the rejection but submit that their current amendment overcomes this rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

IV. Rejection under 35 USC §112, First Paragraph

Claims 1, 6, 8, and 69 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Action asserts that the specification does not provide guidance of the structure of claimed antibody-conjugated dCK fragment as small as two amino acids. Applicants traverse the rejection but submit that current amendment to claim 1 has rendered the rejection moot.

Additionally, the Action asserts that the specification does not provide sufficient teaching on how and where the antibody-conjugated dCK phosphorylates a nucleoside analog. Citing Zhu *et al.*, the Action alleges that undue experimentation is required to determine the function of the conjugate because the specification allegedly does not teach whether and how the conjugate penetrates the nuclear membrane. Applicants respectfully traverse the rejection.

Applicants submit that Zhu *et al.* does not support the assertion that dCK must enter nucleus to phosphorylate a nucleoside analog. On the contrary, Zhu *et al.* teaches that both nuclear and cytosolic dCK can phosphorylate nucleoside analog AraC. *See* Zhu *et al.* Figures 2 and 3. Zhu *et al.* also teach that nucleoside analogs phosphorylated by either nuclear or cytosolic dCK, but not mitochondrial dCK, can be efficiently incorporated into nuclear DNA and cause cell death. See Zhu *et al.* Figure 3. Additionally, Zhu *et al.* teach that a protein is not imported to the mitochondria unless a mitochondria import signal is present. See Zhu *et al.* first paragraph of the Results section and reference cited therein. The specification does not teach, nor does the Action assert, a mitochondria import signal in the dCK conjugate. At the time of the invention, one skilled artisan would have known that, once inside a cell, dCK enhances the toxicity of a nucleoside analog to kill cancer cells by phosphorylating the nucleoside analog. Accordingly, it would not have been undue experimentation to one of ordinary skill in the art to use the conjugate to treat tumor cells.

Based on the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited.

Applicants believe that no fees are due for this Response. If Applicants are mistaken, please charge any requisite fees to our Deposit Account, No. 13-2490.

If there are any questions or comments regarding this Response, the Patent Office is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,
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